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Application of: Mangano

Confirmation No.: 2354

Serial No.: 09/426,792

Group Art Unit: 1614

Filed: October 22, 1999

Examiner: Spivack

For: METHODS FOR REDUCING MORTALITY AND MORBIDITY BY POSTOPERATIVE ADMINISTRATION OF A PHARMACOLOGIC CARDIOVASCULAR AGENT

Attorney Docket No.: 9114-004-999

DECLARATION UNDER 37 C.F.R. §1.132 OF DENNIS T. MANGANO

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dennis T. Mangano, declare that:

1. I am the inventor of the invention claimed in the above-identified U.S. patent application.

2. I earned a Bachelors of Science, (B.S.) *summa cum laude* in electrical engineering in 1965, a Masters of Science (M.S.) in electrophysics in 1967 and a Doctor of Philosophy (Ph.D.) in mathematics and physics in 1971 from Polytechnic Institute of Brooklyn, New York. I received a Medical Doctor (M.D.) from the University of Miami, School of Medicine in 1974. My curriculum vitae is attached hereto at **Exhibit A**.

3. My professional training has included an Internship in internal medicine at the University of Miami Medical Center, Miami, Florida from 1974 to 1975 and a Residency in anesthesia at the University of California, San Francisco, California from 1975 to 1977.

4. I have had a Specialty Certification ("board certified") by the American Board of Anesthesiology since 1978.

5. In my professional capacity I am a professor of Anesthesia and Perioperative Care at the University of California, San Francisco, School of Medicine. I was an Assistant Professor in Residence from 1977 to 1982, Associate Professor in Residence from 1982 to 1987, Vice-Chairman of the Department of Anesthesia from 1986 to 1995, Professor in Residence from 1987 to 1990 and Professor of Anesthesia from 1990 to 1998. I have been on a leave of absence from the University of California from August 1998 to the present.

6. I am also a physician at the Veterans Administration Medical Center in San Francisco, California, serving as Director of the Surgical Intensive Care Unit from 1977 to 1990 and as a full time staff physician from 1977 to 2001.

7. I am the founder of the Multicenter Study of Perioperative Ischemia Research Group (McSPI). The McSPI is a consortium of researchers in approximately 150 centers in the United States, Canada and Europe investigating the predictors of myocardial ischemia, infarction, stroke and renal failure in high risk patients undergoing cardiac and non-cardiac surgery.

8. I am the founder and Chief Executive Officer of the Ischemia Research and Education Foundation, a non-profit biomedical research organization that conducts clinical and scientific research specializing in the problems of morbidity and mortality through the study of perioperative ischemia.

9. I have authored and co-authored over 150 scientific papers that have been published in journals such as, *Journal of the American Medical Association*, *New England Journal of Medicine*, *Annals of Cardiac Anesthesia*, *Journal of the American College of Cardiology*, *Journal of Thoracic and Cardiovascular Surgery*, *Journal of Cardiothoracic and Vascular Anesthesia* and *Stroke* among others.

10. I have reviewed the specification of the above-identified patent application, as well as the claims currently pending in the Application. I have also reviewed the final office action, mailed April 23, 2003 (hereinafter, the "final office action") in connection with the above-identified patent application, and the following references cited

therein:

a. Goldstein *et al.* 1993, *J. Cardiovasc. Pharmacol.* 22(2): 253-258; and

b. Kataria *et al.* 1990, *J. Cardiothoracic Anesth.* 4/5 S2: 13-16.

11. In summary, the reference document Goldstein *et al.* 1993, *J. Cardiovasc. Pharmacol.* 22(2): 253-258, (hereinafter "Goldstein"), does not teach or suggest any treatment with the study medication immediately after surgery. Additionally, I believe that it would have been surprising to one familiar with the field that therapy for cardiovascular diseases be administered continuously, throughout surgery and the entire hospitalization and after hospital discharge. Finally, it would have been surprising to one familiar with the field that therapy for cardiovascular diseases from before surgery to during surgery or immediately after surgery and daily thereafter would be beneficial to patients.

12. I have reviewed the document referred to as Kataria *et al.* 1990, *J. Cardiothoracic Anesth.* 4/5 S2: 13-16 (hereinafter "Kataria"). Kataria does not teach or suggest any treatment with the study medication prior to, during surgery or immediately after surgery and daily thereafter. Additionally, I believe that one familiar with the field would have been surprised that treatment of a surgical patient with a cardiovascular agent prior to the development of postoperative hypertension would be beneficial.

13. I believe Goldstein fails to teach or suggest treatment with a cardiovascular agent prior to or during surgery. Goldstein fails to teach any treatment with the study medication (nebivolol or atenolol) between surgery and a full two hours after extubation. At the time of the Goldstein study, bypass surgery patients were not generally extubated until the following morning after surgery. As a result, patients were generally not extubated until up to 12 to 18 hours after surgery.

14. I believe Kataria also fails to teach or suggest the use of a β-adrenergic receptor antagonist ("β-blocker") prior to, during surgery or immediately after surgery and daily thereafter. Kataria teaches the use of a β-blocker in hypertensive postoperative patients after emergence and recovery from anesthesia following general surgery.

15. Both Goldstein and Kataria fail to teach administration of a cardiovascular agent in patients prior to, during surgery or immediately after surgery and daily thereafter. Rather, both Goldstein and Kataria teach the administration of a cardiovascular agent

after the stresses of surgery have affected the patient. Based on my knowledge and experience, the administration times of the cardiovascular agents taught by Goldstein and Kataria are too late following surgery. It is my belief that within minutes after reducing anesthesia, a patient's sympathetic nervous system responds to the stresses of surgery. These sympathetic responses include increased blood pressure and heart rate and other excitotoxic, inflammatory and thrombogenic responses. The development of postoperative hypertension in patients, as taught by Kataria, indicates that sympathetic responses are already being exerted on the patient. The administration times taught by Goldstein and Kataria are too late to reduce cardiovascular disease complications.

16. Additionally, it is my belief that Goldstein teaches away from the claimed methods in that Goldstein teaches the interruption of all therapy for cardiovascular diseases for a 4 hour period before surgery. This is in contrast to the claimed methods wherein treatment with a cardiovascular agent is given continuously, daily throughout the entire hospitalization and even after hospital discharge. Based on my understanding and experience, one of skill in the art at the time of the filing of the above-identified patent application would be surprised at the beneficial effects of administering a cardiovascular agent continuously, prior to or during surgery or immediately after surgery. Based on my understanding and experience, administration of a cardiovascular agent continuously, prior to or during surgery or immediately after surgery and daily thereafter would be contraindicated in patients prior to the filing of the above-identified patent application.

17. Furthermore, based on my understanding and experience, one of skill in the art would not have been motivated to administer a β-blocker prior to, during surgery or immediately after surgery and daily thereafter to reduce cardiovascular complications prior to the filing of the above-identified patent application. One skilled in the art prior to the filing of the above-identified patent application would believe administration of a β-blocker prior to during surgery or immediately after surgery and daily thereafter to be contraindicated. Thus, treatment of a patient with a β-blocker following surgery would not be conventional as asserted in the final office action.

18. I, the inventor of the invention described and claimed in the above-identified patent application, further declare that all statements made herein of my own knowledge are

true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the above-identified patent application or any patent issuing thereon.

Respectfully submitted,

Date: 10-22-03

Dennis T. Mangano, Ph.D., M.D.